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Plant-Based Bioactive-Loaded Hydrogels for Wound Care: From Formulation to Clinical Translation - A Review

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Abstract: ***Chronic wounds continue to pose a major challenge to global healthcare systems due to their prolonged healing time and complex pathology. While developed nations face substantial economic burdens from wound management, developing countries encounter additional difficulties related to higher prevalence and limited access to advanced treatments. In this context, the incorporation of plant-derived bioactive compounds into three-dimensional hydrogel systems has emerged as a promising strategy for effective wound care. These bioengineered hydrogels offer multifunctional benefits by simultaneously targeting microbial infections, controlling inflammation, and enhancing tissue regeneration in both acute and chronic wounds. This review focuses on recent advancements in natural bioactive-based hydrogel wound dressings, highlighting plant-derived compounds such as curcumin, Aloe vera, Centella asiatica, quercetin, calendula, and berberine. These compounds are incorporated into polymeric matrices composed of materials like chitosan, alginate, gelatin, polyvinyl alcohol, and hyaluronic acid. Such systems can respond to environmental stimuli, including pH variations, temperature changes, and reactive oxygen species, enabling controlled and sustained release of therapeutic agents. Their synergistic interactions enhance antimicrobial efficacy while also supporting angiogenesis and collagen synthesis, thereby improving healing outcomes and reducing dependence on costly synthetic drugs. Emerging technologies such as self-assembling peptide hydrogels, targeted drug delivery systems, and nanoparticle-assisted biofilm disruption are expanding the scope of personalised wound care solutions. A rigorous evaluation through standardised testing protocols and clinical studies is essential to assess parameters such as stability, mechanical strength, biocompatibility, and therapeutic efficacy. These efforts facilitate regulatory approval and the translation of laboratory research into clinical application. This review consolidates current knowledge and provides practical guidelines for the development and characterisation of natural bioactive-loaded hydrogels. It also outlines future research directions for designing cost-effective, efficient, and widely accessible wound-healing systems.***

Keywords: hydrogel wound dressings; natural bioactive compounds; chronic wound healing; targeted drug delivery; antimicrobial effects; self-assembling peptide hydrogels; reactive oxygen species; polymeric networks; collagen synthesis; bioengineered hydrogels.

I. INTRODUCTION

Wound healing represents a complex, multiphase physiological process essential for restoring skin barrier function and tissue integrity following injury, involving four distinct yet overlapping phases—hemostasis, inflammation, proliferation, and tissue remodelling—each characterised by specific cellular activities and molecular signalling pathways crucial for successful tissue repair. During hemostasis, rapid blood vessel constriction and platelet aggregation form a protective fibrin clot that arrests bleeding and establishes a provisional matrix, while coagulation factors facilitate recruitment of inflammatory cells, particularly macrophages, which orchestrate subsequent phases through secretion of pro-inflammatory cytokines and growth factors including TGF-β, PDGF, FGF, and EGF. The inflammatory phase involves neutrophils infiltrating wound tissue within minutes to hours to eliminate bacteria and clear debris while secreting pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), followed by macrophage phenotypic transition from pro-inflammatory M1 to anti-inflammatory M2 phenotype that acts as master effector cells in tissue regeneration, though excessive inflammation damages normal tissues and impedes healing. The proliferative phase, commencing around day 5-7 post-injury, is characterized by fibroblast proliferation and collagen deposition (types I and III), angiogenesis through endothelial cell sprouting and vessel formation, re-epithelialization as keratinocytes migrate from wound edges, and granulation tissue formation, with myofibroblasts mediating wound contraction through coordinated contractile mechanisms while growth factors including VEGF, bFGF, and TGF-β orchestrate cellular communication and tissue regeneration.

The maturational or remodeling phase, commencing around week 3 and potentially extending 12 months or longer, involves collagen restructuring from disorganized type III to organized type I collagen through MMP-mediated ECM remodeling, wound contraction completion, and apoptosis-driven removal of unnecessary cells, with maximal tensile strength achieved approximately 11-14 weeks post-injury though scars permanently retain only ~80% of unwounded skin tensile strength.[1], [2]

However, chronic nonhealing wounds (CNHW) fundamentally differ from acute wounds through their inability to progress through the orderly, timely healing sequence, affecting approximately 2.5% of the total United States population, with prevalence rising to 15% among Medicare beneficiaries exceeding 65 years, imposing over $3 billion annually in costs and representing the single largest medical expense category.[3]

The hydrogel's water-rich three-dimensional structure closely mimics the extracellular matrix composition and provides an ideal milieu for cellular function, resembling the natural tissue microenvironment that supports wound healing progression. Maintenance of moisture through controlled water vapour transmission prevents both desiccation (which impairs epithelialization and induces tissue damage) and maceration (which promotes bacterial proliferation and degrades surrounding tissue). [4] [5]Hydrogel degradation rate profoundly influences cellular sprouting, migration, and secretion of proangiogenic factors critical for wound healing. Thai et al. demonstrated that endothelial cell-mesenchymal stem cell (EC-MSC) spheroids in fully degradable polyethene glycol (PEG)-based hydrogels achieved 3.8-fold and 4.6-fold higher secretion of VEGF and hepatocyte growth factor (HGF), respectively, compared to non-degradable controls, establishing that matrix degradation serves as a critical signal for proangiogenic factor production.[6]

Natural plant-derived bioactive compounds represent a paradigm shift in wound healing therapeutics through multiple strategic advantages over synthetic pharmaceuticals, offering multifactorial benefits through their inherent bioactivity while addressing emerging antibiotic resistance and chronic inflammation challenges.[7] *Aloe vera*, applied topically for over 5,000 years by Egyptians, Romans, and indigenous peoples, continues as a first-line treatment for burns, ulcers, and surgical wounds with extensive clinical safety documentation. *Centella asiatica*, widely integrated into Korean skincare formulations and traditional Ayurvedic medicine for millennia, exhibits excellent dermal tolerability with enhanced wound healing through triterpene-mediated collagen synthesis and angiogenesis promotion. Clinical trial evidence demonstrates that dressing-incorporated *Aloe vera* and *Centella asiatica* achieved significantly faster complete healing of second-degree burns while significantly reducing patient pain and hospital stay duration with no adverse events or toxicity observed.[8][9]

A. Aim and Scope of the Review

This comprehensive review synthesises current evidence on the development, characterisation, and clinical application of bioactive-loaded hydrogel wound dressings incorporating plant-derived natural compounds for accelerated wound healing. The review majorly focuses on cutting-edge research on multifunctional hydrogel matrices integrating natural bioactive compounds as therapeutic delivery systems addressing the complex pathophysiology of acute, chronic, and complex wounds.

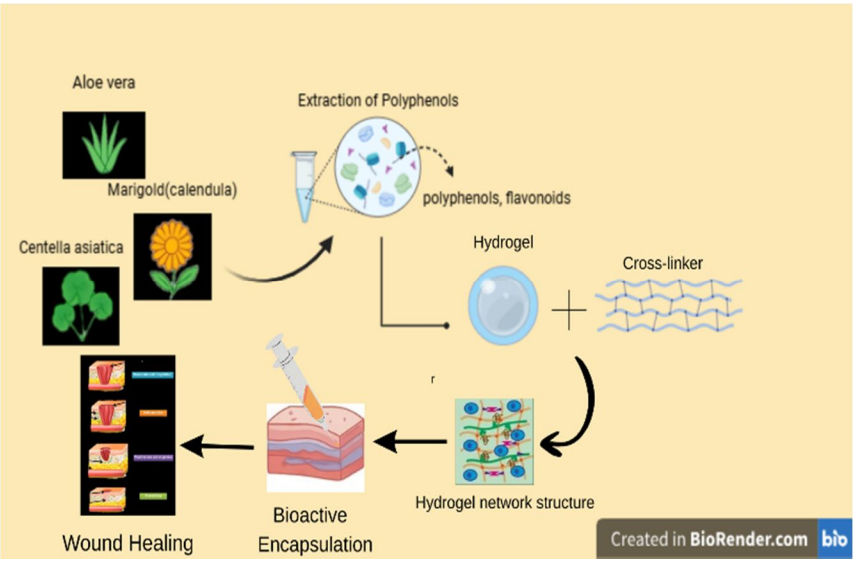

Fig.1.1 Schematic representation of the complete workflow for natural bioactive-loaded hydrogel wound dressings

II. OVERVIEW OF HYDROGELS

Hydrogels are three-dimensional hydrophilic polymeric networks which is capable of absorbing and retaining substantial quantities of water or biological fluids while maintaining their structural integrity, making them ideally suited for wound healing applications. This section mainly focuses on polymer types in hydrogels, their key functional properties, and the usage of bioactive compounds in hydrogels, which are essential for wound healing applications.[10] [11]

A. Various Types of Polymers Used in Hydrogels

Advanced formulations incorporating alginate with dopamine and carboxymethyl chitosan created hydrogels with antibacterial, conductive, adhesive, and self-healing properties, showing photothermal antibacterial effects under near-infrared irradiation with reduced inflammation and enhanced vascular regeneration.[12] Gelatin hydrogels support hemostasis by amplifying the calcium-mediated coagulation cascade, with exceptional hemostatic properties demonstrated in rat wound models. The biocompatibility of gelatin hydrogels was confirmed by minimal hemolysis (0.54% with gelatin in GMA formulations), indicating excellent blood compatibility.[13]

CMC hydrogels significantly regulate transdermal water loss while minimising moisture loss in the wound microenvironment through prominent water-absorbing capacity. Functionally bioadhesion-enhanced CMC/polyvinyl alcohol (PVA) hydrogels, physically crosslinked and chemically modified with citric acid, demonstrated high water retention, hydrophilicity, wettability, permeability, cytocompatibility, and hemocompatibility.[14] PVA-hydroxyethyl starch (HES) blend hydrogels demonstrated that gel fraction increased with increased PVA concentration (maximum 86% with 0% HES) but monotonically decreased with HES incorporation or drug addition, dropping below 40% at 75% HES content. PVA concentration and the freeze-thaw cycle numbers provide control over mechanical properties by eliminating toxic chemical crosslinkers.[15]

B. Multi-Network Hydrogels

Carboxymethyl chitosan/oxidised hyaluronic acid/sodium alginate hydrogels incorporated dual Schiff base and ionic bonding (CMC-HA-SA-TOB system), creating a hybrid network where Schiff base bonds provide chemical crosslinking while ionic bonds from sodium alginate provide stability, enabling pH-responsive release dependent on degradation rather than diffusion where dual-network hydrogels achieve zero-order drug release kinetics, which is ideal for maintaining therapeutic concentrations.[16]

Temperature-responsive systems incorporating poly(N-isopropylacrylamide) segments undergo conformational changes at the lower critical solution temperature (LCST ~32°C), enabling temperature-dependent swelling and drug release adapted to body temperature and inflammatory state.[17]

III. REVIEW OF NATURAL BIOACTIVE AGENTS USED IN HYDROGELS

A. Curcumin (Turmeric)

Composite hydrogels combining guar gum, curcumin-stabilised silver nanoparticles demonstrate exceptional antimicrobial and wound healing synergy.[18]

(GelMA/AHA-Gel@Cur) Combine methacrylated gelatin (GelMA), aldehyde-acylated hyaluronic acid (AHA), and curcumin-coated gelatin nanoparticles through radical polymerisation and Schiff base reactions, creating composite networks with intelligent pH-responsiveness that accelerates drug release in acidic infected wound environments.[19]

B. Aloe vera

Aloe vera-salicylic acid hydrogels prepared using all-green synthesis methods combining salicylic acid, allantoin, and xanthan gum demonstrate good antibacterial properties.[20] 3D-printed Aloe vera-loaded alginate-gelatin hydrogels customised to wound shape provide personalised wound dressing with enhanced macrophage regulation and diabetic chronic wound healing.[21] Acemannan-based hydrogels as purified polysaccharide formulations demonstrate FDA-approved efficacy with defined pharmaceutical specifications.[22]

C. Centella asiatica

PVA/PEG-based hydrogels prepared using freeze-thaw methods incorporate asiaticoside-rich fractions, optimised through Box-Behnken experimental design for gel fraction, swelling index, water vapour transmission rate, and mechanical strength.[23] Collagen-based hydrogels containing Centella asiatica extract with Carbopol 940 show sustained release with high drug entrapment efficiency (82.7% for formulation F3).[24]

Centella asiatica's multi-target approach simultaneously addresses inflammation, collagen synthesis, angiogenesis, and antioxidant protection, providing comprehensive wound care. The four triterpene compounds provide complementary therapeutic effects through distinct mechanisms. Traditional use validation spanning centuries across Asian cultures supports therapeutic credibility. Modern clinical trials increasingly support efficacy claims with innovative delivery systems. The plant is globally available and cost-effective, particularly valuable for resource-limited settings.[25]

D. Quercetin

Quercetin nanocrystal-loaded alginate hydrogels synthesised through nanocrystallization techniques achieve 600-800 nm particle sizes with sustained quercetin release, providing prolonged anti-oxidant activity and rapid wound repair through oxidative stress reduction.[26] Quercetin-loaded liposomal hydrogels incorporating liposomes (carbopol gel base, 15% with varying gelatin ratios) demonstrate multiphase systems with optimised gelatin carbopol ratios (6/4), providing clear, transparent hydrogels.[27] Quercetin-polysaccharide-based hydrogels combine quercetin with natural polysaccharides for sustained antioxidant activity and ROS elimination.[28]

E. Calendula Officinalis (Marigold)

Pullulan/Poly(vinyl alcohol) hydrogels were prepared using an eco-friendly method that combines covalent and physical cross-linking, with calendula hydroalcoholic extract loaded via a simple post-loading immersion method, achieving high loading efficiency due to hydrogen-bonding interactions between the polymer and the extract.[29]

HPMC-based hydrogels with a chitosan delivery system incorporated calendula lyophilised extract at 3% and 10% concentrations, with some formulations including chitosan complexes (extract-chitosan 1:1 ratio) for enhanced delivery.[30]

PVA hydrogel sheets loaded with calendula flower extract were prepared through freeze-thaw cycles, incorporating the extract during hydrogel formation for wound management applications.[31] Bio-adhesive polysaccharides create a protective barrier and maintain an optimal moisture balance for wound healing. Calendula is generally recognised as safe with no significant cytotoxicity reported in therapeutic concentrations.[32]

F. Berberine

Bletilla striata polysaccharide hydrogels were physically blended with varying ratios of BSP and berberine using Carbomer 940; the 2% BSP and BER: BSP ratio of 1:40 showed optimal efficacy.[33] Gelatin/sodium alginate hydrogels carried berberine through dual cross-linking, exhibiting EDTA-induced detachment properties for gentle removal.[34] Gelatin and chitosan-based composite films incorporated berberine hydrochloride and polyelectrolyte, maintaining robust mechanical properties with antimicrobial efficacy >99% following NIR light exposure.[35]

IV. COMPARATIVE DISCUSSION: WOUND HEALING PERFORMANCE OF NATURAL BIOACTIVE COMPOUNDS

This section synthesises comparative performance data across six major phytochemical agents, analysing their in vivo efficacy, mechanistic pathways, and clinical applications for diverse wound types.

Table 1: Comparative Wound Healing Performance of Natural Bioactives with Hydrogels

Bioactive Compound	In Vivo Efficacy	Key Mechanisms of Action	Wound Type Application	Citation
Curcumin (Turmeric)	78% healing efficacy within 7 days	• Collagen synthesis acceleration (day 3 onwards, sustained 3 weeks) • Antimicrobial activity (Gram+ and Gram-), • pH-responsive release in acidic infected environments • ROS elimination	Acute and chronic diabetic wounds; infected wounds	[18]

Aloe Vera	97% complete healing by day 20 11% superior to commercial products	• Macrophage regulation and phenotypic modulation • Anti-inflammatory cytokine reduction (TNF-α, IL-6, IL-1) • Complete re-epithelialization • Organised collagen deposition	Burns, ulcers, surgical wounds, acute wounds	,[20][21]
Centella Asiatica	Clinically demonstrated faster complete healing of 2nd-degree burns; Significantly reduced pain	• Triterpene-mediated (asiaticoside, madecassoside, asiatic acid, madecassic acid) collagen synthesis • Angiogenesis promotion • Multi-target therapeutic approach (inflammation suppression, collagen I & III synthesis, angiogenic factor secretion, antioxidant protection)	Acute, chronic, complex, infected wounds; hypertrophic scars and keloids	[23][25]
Quercetin	91% wound closure by day 14; Scar elevation index 0.18 vs 0.45 (controls) - 60% scar reduction	• ROS scavenging and antioxidant activity • Macrophage M2 polarization (CD206 expression increased 3.2-fold) • TGF-β-Smad pathway regulation • Organised collagen deposition	Acute wounds with reduced scarring potential wounds requiring minimal scar formation	[27]
Calendula Officinalis (Marigold)	89% wound closure by day 14 vs 68% untreated controls (31% improvement) Complete epithelialization and enhanced collagen deposition	• Anti-inflammatory activity through flavanoid compounds • Macrophage proliferation suppression • Exudate formation reduction • Bioadhesive polysaccharide barrier formation	General wound management; anti-inflammatory wound care; cosmetic applications	[29][31]
Berberine	99% bacterial killing efficacy (S. aureus and E. coli); 99% antimicrobial efficacy with NIR light exposure; 89.5% cumulative release over 72 hours	• Antimicrobial activity through dual-network hydrogel systems • Synergistic interaction with Bletilla striata polysaccharides • NIR light-responsive antimicrobial activation • Biofilm penetration and disruption	Infected wounds; multidrug-resistant bacterial infections; chronic infection-prone wounds	[34][35]

V. CHARACTERISATION AND FORMULATIONS

The successful incorporation of bioactive-loaded hydrogels from laboratory to clinical applications requires rigorous characterisation using standardised methodologies that assess both physicochemical properties and biological performance.

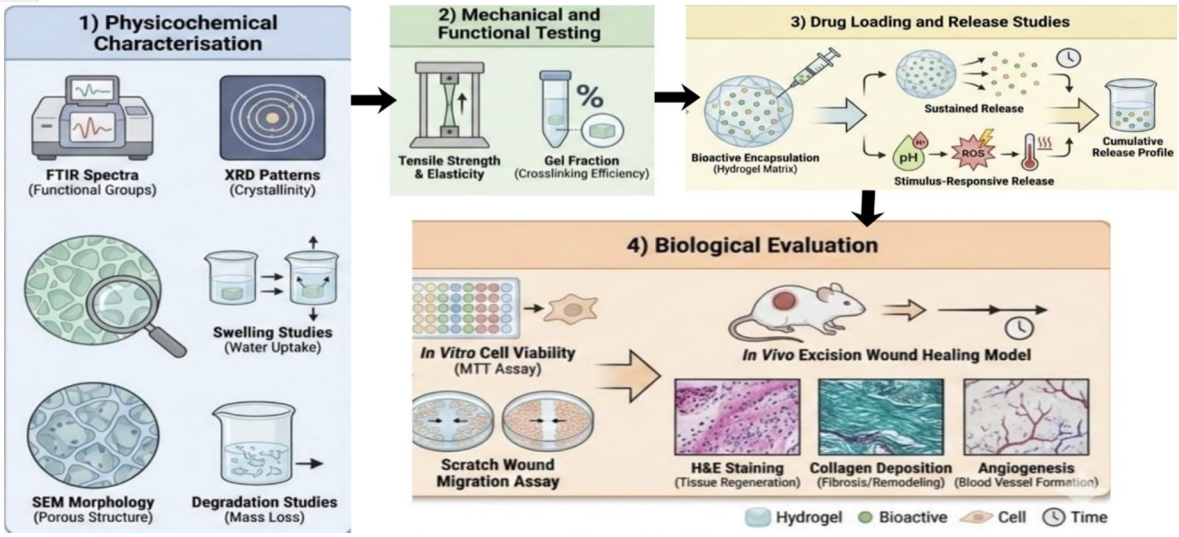

Fig.5.1 Schematic representation of the comprehensive characterisation and evaluation strategies assessed in natural bioactive-loaded hydrogel wound dressings, including physicochemical, mechanical, drug release, and biological assessments required for successful translational applications.

A. Common In Vitro and In Vivo Models

1) In Vitro Cellular Models

Scratch Wound Assay (Cell Migration Assay)

This two-dimensional method involves creating a cell-free gap in a confluent monolayer of keratinocytes (HaCaT cells) or fibroblasts (L929, NIH3T3, or human dermal fibroblasts) using sterile pipette tips or specialised wound-making tools.[36]

2) Cell Viability and Proliferation Assays

Cells are exposed to various concentrations of hydrogel extracts (typically 12.5-400 µg/mL) for 24-48 hours, followed by MTT reagent addition and spectrophotometric measurement at 570 nm. [37]

B. Characterisation Methods

1) Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy confirms successful incorporation of bioactive compounds and crosslinking in hydrogels through identification of characteristic functional groups. Spectra are typically recorded in the range 4000-400 cm^{-1} using attenuated total reflectance (ATR) mode. The peaks shown for polysaccharide-based hydrogels include: O-H stretching (3200-3400 cm^{-1}), C-H stretching (2800-3000 cm^{-1}), amide I band (1650 cm^{-1}), and for amide II band (1550 cm^{-1}).[38]

2) X-Ray Diffraction (XRD)

XRD analysis determines crystallinity and confirms drug encapsulation within the hydrogel matrix. The disappearance or reduction of characteristic crystalline peaks of bioactive compounds indicates successful molecular dispersion or amorphisation within the polymer matrix.[35]

C. Bioactive Compound-Specific Formulations

1) Curcumin (Turmeric)

Chopra et al. developed chitosan-PVA-curcumin hydrogels with varying ratios, achieving sustained release profiles and significant antimicrobial activity against both Gram-positive and Gram-negative organisms, as demonstrated by molecular docking studies showing strong binding to inflammatory proteins. The optimal formulation exhibited dissolution characteristics enabling controlled curcumin delivery while maintaining bioactivity.[39] Algahtani et al. formulated curcumin nanoemulgel systems that demonstrated superior ex vivo skin permeability, with flux values of 285.3 ± 12.4 µg/cm^2/h. In vivo excision wound studies in Wistar rats showed 78% wound healing efficacy within 7 days, with histopathological analysis confirming enhanced collagen fibre formation, complete stratum corneum development, and presence of sebaceous glands and hair follicles, indicating functional skin regeneration.[40]

2) Aloe Vera

Chelu et al. studied aloe vera hydrogel formulations that highlight the mechanisms of antimicrobial activity and anti-inflammatory effects through cytokine modulation. Antibacterial aloe vera biocompatible hydrogels developed by combining 5-10% aloe vera gel with polyvinyl alcohol and cross-linking agents exhibited pH values of 5.81-5.96, matching the skin's natural pH. The formulations exhibited no deformation under the vial inversion test, confirming adequate gel strength. In vivo rat wound models showed 97% complete healing by day 20 with aloe vera-loaded hydrogels, compared to 86% with commercial products, with histological examination revealing organised collagen deposition and complete re-epithelialization.[41] Singh and colleagues explored bioactive aloe vera and sterculia gum network hydrogels, achieving swelling ratios of 450-800% in physiological conditions. Incorporation of zinc oxide nanoparticles in hydrogels enhanced antimicrobial properties while maintaining biocompatibility, with MTT assays showing >85% cell viability at concentrations up to 200 µg/mL [42]

3) Centella Asiatica

Witkowska et al. developed chitosan-based hydrogels for the controlled delivery of Centella asiatica extract, using Design of Experiments (DoE) optimisation approaches. The optimised formulation containing 3% extract with 3% medium-molecular-weight chitosan demonstrated controlled asiaticoside release with PAMPA skin permeability coefficients of 4.2×10^{-6} cm/s, indicating excellent skin penetration potential. They also observed synergistic antimicrobial activity, with minimum inhibitory concentrations (MIC) which is around 64-128 µg/mL against *S. aureus* and *E. coli*. Their hydrogel exhibited hyaluronidase inhibition activity (IC_{50} = 185 µg/mL), crucial for preventing excessive inflammation and promoting organised collagen deposition.[38]

4) Quercetin

Jangde et al. developed quercetin-loaded liposomal hydrogels incorporating 15% carbopol with varying gelatin ratios (6:4 carbopol: gelatin optimal). The multiphase system achieved encapsulation efficiency of 78.5% with controlled release showing 82% cumulative drug release over 48 hours following the Higuchi kinetic model (R^2 = 0.9847). Water vapour transmission rate of 2145 g/m²·24h provided optimal moisture balance. Hemocompatibility testing showed <3% hemolysis, while in vivo rat wound studies demonstrated accelerated closure with a significant decrease in healing time (complete closure by day 12 versus day 18 for controls).[43]

Yang et al. and their team developed gallium-modified gelatin nanoparticles loaded with quercetin demonstrated synergistic antimicrobial and healing-promoting effects. The hydrogel achieved bacterial inhibition of 99.5% against *S. aureus* and 97.8% against *E. coli* within 24 hours. Mechanism-based studies revealed regulation of macrophage polarisation through TGF-β/Smad pathway, which promotes the M2 phenotype ($CD206^+$ expression increased 3.2-fold), which is essential for tissue remodelling. In vivo evaluation showed 91% wound closure by day 14 with reduced scar formation (scar elevation index 0.18 versus 0.45 for controls).[44]

5) Calendula Officinalis (Marigold)

Polyacrylamide hydrogels containing calendula extract were prepared by Ferreira et al., and their team characterised the formulations through FTIR, SEM, and biological assays. The hydrogels demonstrated anti-inflammatory activity attributed to flavonoids (specifically rutin content 4.2% w/w of extract), with significant reduction in macrophage proliferation and exudate formation in wound sites.[32]

Calendula flower extract-loaded PVA hydrogel sheets were developed through optimisation studies employing factorial design approaches. The optimal formulation contained 5% calendula flower extract with 10% PVA, crosslinked through freeze-thaw cycling (5 cycles). Characterisation studies revealed suitable mechanical properties (tensile strength around 0.85 MPa, and elongation about 145%), adequate swelling ratio (450%), and controlled drug release (72% over 48 hours). In vivo evaluation in albino rats also demonstrated 89% wound closure by day 14 compared to 68% for untreated controls, with enhanced collagen deposition and complete epithelialization.[31]

6) Berberine

Hu et al. developed berberine-loaded *Bletilla striata* polysaccharide (BSP) hydrogels using Carbomer 940 as a gelling agent, optimising formulations through systematic screening. The optimal LBSP/BER hydrogel, which is around (2% BSP, 1:40 berberine: BSP mass ratio) and exhibited a viscosity of 78,208 mPa·s and excellent water retention capacity (>60% moisture retention after 48 hours).

FTIR and DSC analyses confirmed their successful drug-polymer interactions without chemical degradation. In vitro release studies also showed a biphasic profile, with 45% release in the first 6 hours, followed by sustained release, reaching 85% cumulative release by 48 hours, consistent with the Korsmeyer-Peppas model (n = 0.58).[33]

Akhter et al. formulated a berberine-encapsulated polyelectrolyte nanocomposite gel using the chitosan-alginate ionic gelation method, followed by the incorporation of Carbopol gel. The Box-Behnken design optimisation approach yielded nanoparticles with a size of 71 ± 3.5 nm, PDI of 0.45, zeta potential of +22 mV, and encapsulation efficiency of 91 ± 1.6%. The developed nanocomposite gel demonstrated optimal consistency, spreadability (12.5 g·cm/s), and extrudability, making it suitable for topical application. Drug release at pH 6.8 (which simulates wound microenvironment) showed around 89.5 ± 6.9% cumulative release over 72 hours.[35]

VI. CHALLENGES AND FUTURE PERSPECTIVES

A. *Limitations and Challenges in Current Research*

Huynh et al. identified that hydrogel dressings currently face several challenges, including high costs, low durability, and the risk of infection and allergies, with universal efficacy in treating all categories of wounds not yet fully established. The difficulty is mostly from the complex interconnection between polymer composition, their crosslinking density, and the physiological microenvironment where the hydrogel must function.[45]

High water content (80-90%) necessary for maintaining a moist wound microenvironment typically compromises mechanical properties, limiting the hydrogel's ability to withstand manipulation during application and removal. Conversely, improving mechanical strength often necessitates increased crosslinking density, which may impede cell infiltration, nutrient diffusion, and exudate absorption—key functions for effective wound healing.[46][47]

Wroe et al. reported that bacteriophage-encapsulating hydrogels achieved around 4.7-fold reduction in live *Pseudomonas aeruginosa* counts compared to controls, which highlights the necessity for alternative antimicrobial approaches beyond conventional antibiotics. The non-fouling properties of hydrogels, while beneficial for reducing non-specific adsorption, paradoxically complicate biofilm formation and subsequent antimicrobial testing, requiring specialised microfluidic devices to simulate realistic wound conditions.[48]

Laurano et al. highlighted that identification of standardised procedures to prepare and characterise advanced wound dressings is extremely complex, with the characterisation techniques commonly used for traditional wound dressings often inadequate for assessing the superior capabilities of advanced platforms in enhancing wound healing. Advanced characterisation should simultaneously investigate tissue regeneration rate, drug release effectiveness, and electronic control of on-demand drug delivery mechanisms while avoiding dependence on boundary conditions.[47]

Kawee-ai et al. addressed the challenge of bioactive compounds' stability in natural extract-loaded hydrogels, where many bioactive compounds, such as phenols, flavonoids, and essential oils, are highly sensitive to environmental factors, including light, heat, and oxygen. This sensitivity leads to degradation during gel preparation, storage, and application, reducing efficacy—a particular concern for polyphenolic compounds like curcumin and ascorbic acid, prone to oxidative degradation.[49]

Zamora-Mendoza et al. documented that extract release from hydrogels is influenced by extract solubility and hydrogel size/shape, with release profiles differing significantly between similar formulations containing different extraction methods. Cotton cellulose vs microcrystalline cellulose hydrogels loaded with plant extracts demonstrated extract release ranging from <30% to 80%, highlighting the profound impact of polymer properties on bioavailability.[50]

B. *Emerging Technologies*

Wu et al. developed ROS-reactive injectable glycopeptide hydrogels based on phenylboronic acid-grafted oxidative glucan (POD) and caffeic acid-grafted ε-polylysine (CE) for chronic diabetic wound healing. Mangiferin (MF), an antioxidant compound, was loaded into the hydrogel, with boronate-ester bonds undergoing cleavage in response to elevated ROS levels, enabling continuous MF release that suppressed inflammation and promoted healing in infected diabetic wounds.[51]

Qiao et al.'s ROS-responsive HA-PBA/PVA hydrogel with sequential moxifloxacin and curcumin delivery represents the first successful spatiotemporally sequential delivery system for treating MRSA-infected wounds. The differential approach of loading the hydrophilic and hydrophobic drugs within distinct matrix compartments, which creates spatial separation, results in temporal differences in release rates that match different treatment phases where rapid antibiotic release is followed by sustained anti-inflammatory effects.[52]

Makabenta et al. demonstrated that antimicrobial polymeric nanoparticles (PNPs) incorporated into Poloxamer 407 hydrogels achieved 99% bacterial biofilm clearance, with PNPs demonstrating exceptional biofilm penetration and disruption of resistant and persistent cells within biofilm matrices. PNPs did not obtain resistance even after multiple exposures to sub-therapeutic doses, distinguishing them from conventional antibiotics. In vitro studies revealed that PNPs significantly reduce prolonged inflammation associated with infection while promoting fibroblast migration, establishing dual antimicrobial-immunomodulatory properties.[53]

C. Future Perspectives

Guan et al. comprehensively reviewed self-assembling peptide (SAP)-based hydrogels for wound healing, highlighting their innate biocompatibility, biodegradability, ligand-receptor recognition capabilities, stimulus-responsive self-assembly, and ability to mimic the extracellular matrix. The peptide-based fibrous network structure resembles fibrin in the extracellular matrix, facilitating damaged tissue repair and biological function restoration.[54]

Veith et al. comprehensively reviewed therapeutic angiogenesis strategies in wound healing, emphasising that neovascularisation represents a critical wound healing stage requiring sophisticated assessment methodologies. Development of injectable hydrogels is derived from natural polymers, which promote therapeutic neovascularisation by both intrinsic properties and sustained growth. Acidic-based gelatin hydrogels loaded with basic fibroblast growth factor (bFGF) demonstrated prolonged neovascularisation in mouse models, with vascularisation that can be modified by adjusting hydrogel water content.[55]

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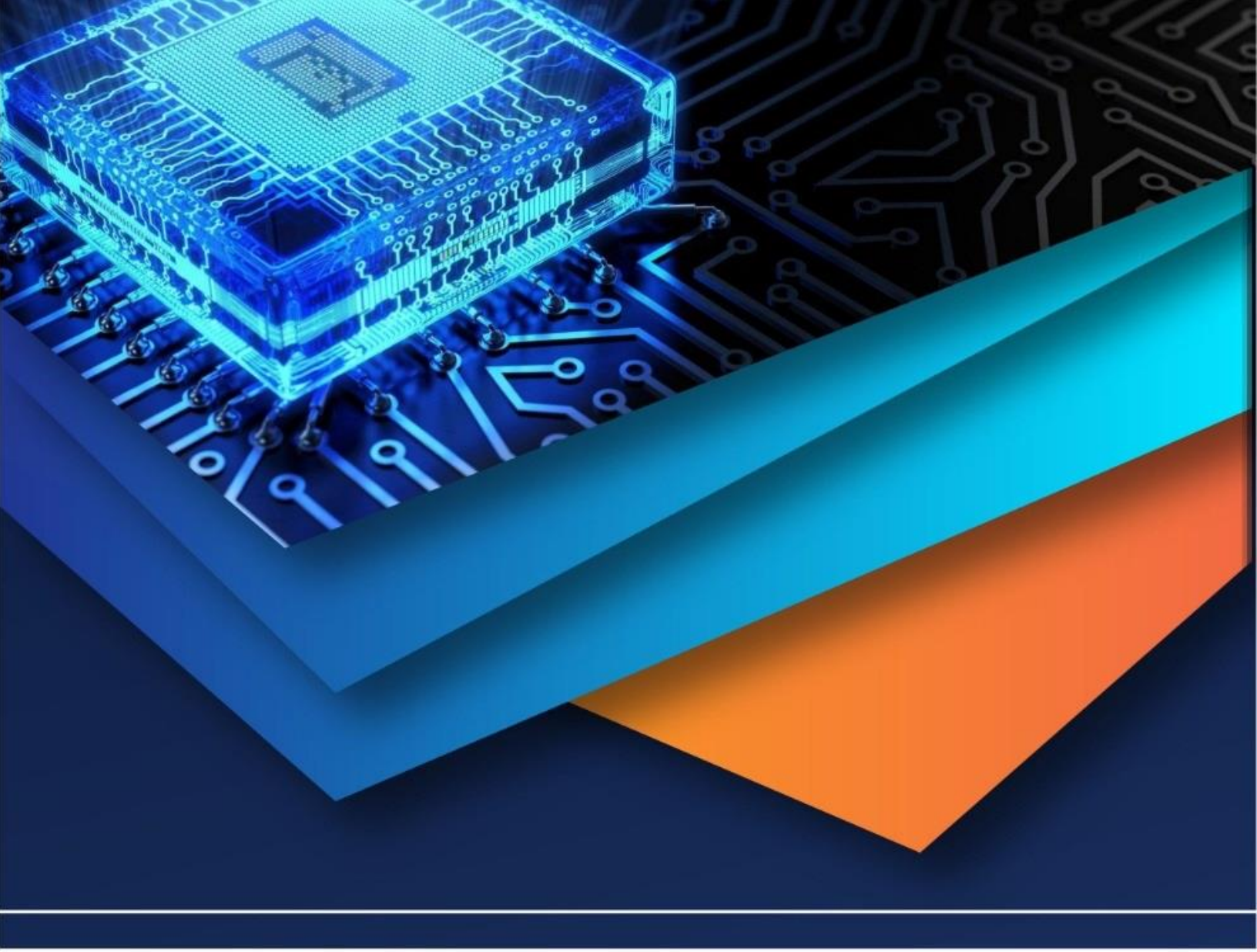

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